Metabolic dysfunction-associated fatty liver disease: from basic research to clinical application

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The increasing burden of non-alcoholic fatty liver disease: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the world. NAFLD encompasses a spectrum of liver disease, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). With the pandemic of obesity and type 2 diabetes mellitus (T2DM), there has been an exponential growth in the prevalence of NAFLD over the past two decades. The prevalence of NAFLD in most Asian countries, including China, is above 25% in the general adult population.[1] Furthermore, there is a developing childhood obesity pandemic, and a meta-analysis of 20,595 children in Asia generated a pooled NAFLD prevalence of 5.53%, which had increased by approximately 1.6-fold since 2010. The pooled prevalence of NAFLD in Asian children increased from those with normal weight (1.5%) to those who were overweight (16.7%) or obese (50.1%).[2]

A recent study suggested that NAFLD is not uncommon in lean Chinese adults with a normal waist circumstance. Metabolic risk factors, rather than genetic factors, may play an important role in the development of lean NAFLD,[3] and the hepatic and extra-hepatic complications can also develop in lean patients, which reinforces the importance of considering metabolic phenotype in the assessment of NAFLD, rather than using body mass index-based approaches.[4]

Renaming of NAFLD to MAFLD: A diagnosis of NAFLD is made on the basis of histological or imaging-derived evidence of steatosis, in the absence of a known etiology of fatty liver. With advances in knowledge of the pathogenesis of the condition, the "exclusive" term NAFLD no longer serves to precisely describe a highly heterogeneous disease. In 2020, the novel term of metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed in an attempt to create an "inclusive" diagnosis.[5] Zeng *et al*[6] performed a cross-sectional study of Chinese adults which showed that the prevalence of MAFLD is higher than that of NAFLD, and therefore the newly-defined label of MAFLD may better reflect the metabolic pathogenesis. Furthermore, a pathologic analysis of patients with MAFLD showed that a single metabolic defect can have a significant role in the development of fibrosis and that insulin resistance plays a key role in the progression of steatohepatitis and the development of significant fibrosis.[7]

As Zheng *et al* discussed, by using the new terminology, "cryptogenic cirrhosis" and MAFLD can now be diagnosed in lean individuals using metabolic criteria, rather than being viewed as completely separate entities. The renaming of NAFLD to MAFLD may result in significant improvements in awareness, advocacy, research, and the clinical management of the condition.[8]

Update on the pathogenesis of MAFLD: The pathogenesis of NAFLD/MAFLD is a multifactorial process, involving interactions among nutrition, metabolism, genetic predisposition, the gut microbiota, and environmental factors. Although a great deal of progress has been made in recent decades, the pathogenic mechanism of NAFLD/MAFLD has yet to be fully elucidated. In this issue of the *Chinese Medical Journal* (*CMJ*), Pan *et al*[9] give an overview of the role of hepatocyte nuclear factor 4α (HNF4α) in the pathogenesis of NAFLD. HNF4α has been shown to regulate bile acid, lipid, and glucose metabolism; and hepatic HNF4α expression is much lower in patients with NAFLD and mouse models of NASH. Furthermore, there is evidence that hepatic HNF4α plays a key role in the initiation and progression of NAFLD and may represent a therapeutic target for NAFLD.[9]

Huang *et al*[10] presented a systematic review regarding the role of retinol-binding protein 4 (RBP4) in the development of NAFLD and its potential therapeutic application. RBP4 induces hepatic *de novo* lipogenesis, impairs fatty acid oxidation, increases insulin resistance, and promotes hepatic inflammation. Furthermore, a high plasma RBP4 concentration is associated with a high risk of NAFLD; and agents that reduce the circulating RBP4 concentration and/or hepatic RBP4 expression have a protective effect against NAFLD. These findings suggest that RBP4 could be targeted as a novel diagnostic marker or therapeutic target for NAFLD.[10]

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Jackson *et al*[11] summarized the essential physiology of bile acid and sphingolipid metabolism, because the dysregulation of both are potential contributors to NAFLD. Specifically, the dysregulation of bile acid and sphingolipid metabolism has been linked to hepatic steatosis, inflammation, and fibrosis, and the further exploration of the pathologic effects mediated by bile acids and sphingolipids may also lead to new diagnostic and therapeutic strategies for NAFLD.

Hepatitis B and concurrent MAFLD: Concomitant NAFLD/MAFLD in patients with chronic hepatitis B (CHB) has become highly prevalent over the past two decades. However, the risks associated with the dual etiologies, outcomes, and mechanisms involved in the interaction between CHB and NAFLD have not been fully characterized. Tong *et al*[12] summarize the findings of recent clinical and basic research studies related to the potential interactions between CHB and NAFLD. The prevalence of hepatic steatosis in CHB has been reported to be 32.8% (95% CI, 28.9%–37.0%); and it is higher in men and patients with obesity. The presence of hepatic steatosis in patients with CHB is related to metabolic, rather than viral factors. Patients with both CHB and NAFLD are more likely to experience liver-related outcomes or death than those with CHB alone. Many studies have shown that steatosis is positively associated with the clearance of hepatitis B virus (HBV) surface antigen and a reduction in HBV DNA, and the prevalence and incidence of NAFLD in patients with CHB may be lower than in those without.

In Chang and colleagues' multi-center, prospective study of 1000 treatment-naïve patients with biopsy-confirmed CHB, NASH was found in 182 patients (18.2%), 46% of these achieved resolution of NASH, and only 4% of the patients developed new-onset NASH after 72 weeks of entecavir treatment. Body mass at baseline and a slight weight change during follow-up were associated with the prevalence, incidence, and remission of NASH in patients with CHB.[13] Finally, steatosis is more prevalent in patients with CHB and is a common reason for abnormal circulating liver enzyme activities in infected patients with a low HBV-DNA load or a good response to infection.

From MAFLD to HCC: Although viral hepatitis remains the most common etiology of liver cancer-related deaths, NAFLD is the most rapidly growing contributor to mortality and morbidity related to liver disease in the world. The global burden of HCC is increasing alongside the NAFLD pandemic. A recently published review in *CMJ* summarizes the characteristics of NAFLD-related HCC.[14] The incidence of NAFLD-related HCC is much higher in patients with severe steatohepatitis, advanced fibrosis, and cirrhosis than in individuals with NAFLD in general, and it is most likely to occur in older men with metabolic syndrome. The incidence of HCC in patients with NAFLD-related cirrhosis is lower than that in those with hepatitis C virus- or HBV-related cirrhosis. Compared with HCCs of other etiologies, NAFLD-related HCCs are generally large, well-differentiated, solitary lesions with a higher level of inflammatory infiltration, and they are less likely to metastasize extra-hepatically. Moreover, NAFLD-related HCC is more likely to develop in the absence of cirrhosis.[14] In a recent issue of *CMJ*, Rios *et al* reviewed the progression of MAFLD to HCC and stated that lipotoxicity, insulin resistance, oxidative stress, chronic inflammation, multiple gene mutations, and alterations to the fecal microbial composition are the most important factors determining hepatic carcinogenesis, whereas steatohepatitis and fibrosis are not essential for the development of HCC in obesity-related fatty liver disease.[15]

Non-invasive diagnosis of MAFLD: Accumulating evidence suggests that non-invasive tests can be used to diagnose NAFLD, assess its severity, and predict its prognosis. In a recent issue of *CMJ*, Li *et al* review new developments in non-invasive testing for NAFLD, with respect to steatosis, steatohepatitis, and fibrosis.[16] For the identification of steatosis, ultrasonography remains the most common method, because of its wide availability and low cost, but magnetic resonance imaging-proton density fat fraction is currently the most accurate means of identifying hepatic steatosis, and transient elastography (TE) represents a promising technique for the evaluation of hepatic steatosis and fibrosis. Except for the widely used controlled attenuation parameter, ultrasonographic attenuation has been reported to have a low failure rate and shows moderate-to-high performance for the discrimination of degrees of steatosis in patients with chronic liver disease.[17]

Various non-invasive algorithms, such as the fatty liver index (FLI) and hepatic steatosis index (HSI), have been used as screening tests for steatosis in epidemiologic studies. In Chen et al's study, both FLI and HSI were shown to be useful screening tools for NAFLD in adults with obstructive sleep apnea/hypopnea syndrome.[18] In patients with steatohepatitis, some circulating biomarkers correlate with the severity of NASH but show modest predictive accuracy. Regarding liver fibrosis, liver stiffness measurement (LSM) using TE is highly accurate and is widely used worldwide. Magnetic resonance elastography is marginally better than TE, but it is limited by its cost and availability. In contrast, simple fibrosis scores, such as the fibrosis-4 (FIB-4) index and the NAFLD fibrosis score, can be easily calculated and are recommended for use in primary care. These scores and LSM have sufficiently high negative predictive values to exclude advanced fibrosis. Recently, Shi *et al* found that the combination of the presence of a metabolic disorder and the FIB-4 index provides for a more accurate diagnosis of advanced fibrosis in patients with NAFLD.[19] Thus, as part of the redefinition of MAFLD, metabolic risk factors should be taken into account during diagnosis and management.

Therapeutic approaches to MAFLD: In a recent issue of *CMJ*, Shi *et al*[20] discuss recent advances and provide a perspective regarding the treatment of MAFLD. Weight management through an appropriate diet and physical activity remains the most important component of the treatment of MAFLD. Weight loss through bariatric surgery may be an effective means of achieving significant improvements in patients with morbid obesity and MAFLD. Although numerous agents, including novel modulators of glucolipid metabolism, are being assessed in clinical trials, there is still no approved drug for the treatment of MAFLD. The nomenclature of MAFLD emphasizes the existence of concomitant metabolic disorders and obesity, and patients with MAFLD are therefore subject to both hepatic and other

metabolic risks. Thus, drugs targeting underlying cardiometabolic risk factors are essential to improve the outcomes of patients with MAFLD.

The screening of patients who are at a high risk of MAFLD and the provision of a comprehensive individual therapeutic program are critical. For example, patients with MAFLD and T2DM would benefit from the use of antidiabetic agents, patients with overweight or obesity would gain greater benefit from weight management, and those with metabolic syndrome require comprehensive individualized management. These therapeutic approaches might help identify the patients with MAFLD who are at the greatest risk of disease progression and facilitate more precise and appropriate management.

Summary and prospects: The growing burden of NAFLD parallels the increasing prevalences of obesity and metabolic syndrome worldwide. Cardiometabolic risk factors have a bidirectional relationship with NAFLD. The majority of patients with NAFLD meet the diagnostic criteria for MAFLD, and this represents a more appropriate term. Further clinical studies of the changes created by the redefinition of NAFLD/MAFLD, including the epidemiologic character, prognosis, diagnosis, prevention, and treatment of the condition, are required. Currently, MAFLD and CHB are increasingly being diagnosed in the same individuals, and the pathophysiological interaction between MAFLD and HBV infection in patients is worthy of further exploration. The long-term outcomes of MAFLD are related to the severity of metabolic dysfunction and liver fibrosis, rather than obesity. Metabolic syndrome and T2DM are the most important risk factors for MAFLD-related cirrhosis and HCC. A lack of awareness regarding the factors underlying MAFLD-related HCC may lead to delay in its diagnosis.

The further development and validation of non-invasive diagnostic techniques and clinical pathways will help clinicians assess the severity of MAFLD, categorize patients, and identify those requiring specific treatments. There is still no effective approved drug for MAFLD, but the in-depth study of pathologic mechanisms may provide new therapeutic targets. Measures to increase awareness and treat or prevent the associated cardiometabolic diseases are necessary to reduce the growing burden of MAFLD.

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Conflicts of interest

None.

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